from the group consisting of penicillin, streptomycin, hingizone, non-essential amino acids, sodium pyruvate, and fetal bovine serum, said concentration being effective for promoting or enabling cellular growth and respiration.

REMARKS

Claims 1-12, 14-16, 49-62 and 91-102 are in the present application.

In the Official Action of March 29, 2002 the following issues have been raised: (i) 35 U.S.C. Section 102(b) claim rejections, (ii) 35 U.S.C. Section 103(a) claim rejection, (iii) 35 U.S.C.Section 112, second paragraph claim rejections, and (iv) objection to Title of specification. These issues are addressed below.

(i) 35 USC 102 Rejections

In the present Official Action, the Examiner has rejected Claims 1-4, 6-7, 13, 49-52, 54-55, and 59 under 35 USC 102 (b) as allegedly being anticipated by Bacon. Additionally, the Examiner has rejected Claims 1-4, 10, 13, 49-52, 58, and 59 under 35 USC 102 (b) as allegedly being anticipated by Parker. The Examiner has alleged that "all the features of the claims are taught by the above references for the same functions as claimed." Applicants respectfully submit that these rejections do not anticipate the claimed invention. For a reference to anticipate a claim, the reference must contain all of the elements of the claim[1]. Moreover, the single source must disclose all of the claimed elements, "arranged as in the claim.[2]"

Bacon teaches only immobilizing $[Ru(Ph_2phen_2)](ClO_4)$ in polymers. Bacon does not teach or suggest the present invention as claimed. In particular, Bacon does not teach or suggest determining the presence or absence of enzymatic reactions in solution, or the method of comparing the value of luminescence in an "experimental" to that of a "control", and repeating the measurement as needed to determine the presence (or

[1] See Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1379 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); Atlas Powder Co. v. E.I.. du Pont De Nemours & Co 750 F.2d 1569, 1574, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984); In re Marshall, 578 F.2d 301, 304, 198 U.S.P.Q. 344, 346 (C.C.P.A. 1978).

absence) of oxidative reactions as claimed in steps (iv) or (v) of Claims 1 and 49. Thus Bacon does not anticipate independent Claim 1, which recites that (a) the enzyme is in solution and (b) the comparison with a control. Similarly, Bacon does not anticipate independent Claim 49 which recites (a) enzyme(s) in solution, (b) a sensor composition not in contact with the solution and (c) the comparison with a control, since Bacon does not contain all of the elements of the claim and does not disclose all of the claimed elements arranged as in Claim 49.

Parker only teaches immobilized glucose oxidase (GOx) whereas the claimed invention sets forth methods for determining presence or absence of oxidative reactions catalyzed by at least one enzyme in a solution. Parker (on p. 158, third paragraph) states that the enzyme supplier, Sigma's, procedure was followed, except that the solution of glucose oxidase was "replaced with the immobilized enzyme", that being defined by Parker to be GOx entrapped within polymerized PHEMA. This teaches directly away from the use of this system for "free" redox-capable enzymes in solution. The statement by Parker, and clearly within the context of Parker's teachings, demonstrates to one of oprdinary skill in the art taht the enzymatic redox reactions cannot be monitored when such enzymes are in solution. Further, Parker does not teach or suggest the method of comparing the value of luminescence in an "experimental" to that of a "control", and repeating the measurement as needed to determine the presence (or absence) of oxidative reactions as claimed in steps (iv) or (v) as recited in Claims 1 and 49. Thus Parker does not anticipate Claim 1 which recites (a) the enzyme in solution and (b) the comparison with a control because Parker fails to contain all of the elements of the claim and disclose all of the claimed elements arranged as in the claim.

Parker also states (first paragraph of page 161) that "...an aqueous solution of glucose cannot be measured using a hydrophobic matrix.", where Parker's hydrophobic matrix is defined as a poly(dimethylsilicone) rubber matrix (PDMS) similar to that of the applicants. As the reaction of glucose with the enzyme glucose oxidase consumes

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[2] Richardson v. Suzuki Motor Co. 868 F.2d 1226, 1236, 9 U.S.P.Q. 2d 1913, 1920 (Fed. Cir. 1989); Connell v. Sears Roebuck & Co., 722 F.2d 1542, 1548, 220 U S.P.Q. 193, 198 (Fed. Cir. 1983).

oxygen it is thus an oxidative reaction. Thus, Parker again does not anticipate Claim 49 which recites (a) enzyme(s) in solution, (b) a sensor composition not in contact with the solution and (c) the comparison with a control because Parker fails to contain all of the elements of the claim and disclose all of the claimed elements arranged as in the claim.

Although Claims 1-4, 6-7, 49-52, 54-55 and 59 have been rejected as anticipated under 35 USC Section 102(b) under the disclosure of Bacon and Claims 1-4, 10, 49-52, 58 and 59 have been rejected under the disclosure of Parker, it is axiomatic that anticipation under Section 102 requires that the prior art reference disclose every element of the claim. In re King, 801 F.2d 1324, 1326, 231 U.S.P.Q. 136, 138 (Fed. Cir. 1986). Thus there must be no differences between the subject matter of the claim and the disclosure of the prior art reference. Stated in another way, the reference must contain within its four corners adequate directions to practice the invention. The corollary of this rule is equally applicable. The absence from the reference of any claimed element negates anticipation. Kloster Speedsteel AB v. Crucible Inc., 793 F.2d 1565, 1571, 230 U.S.P.Q. 81, 84 (Fed. Cir. 1986).

Here it is clear that independent Claims 1 and 49 as amended and all claims dependent thereon differ from Bacon and Parker. Clearly Kloster Speedsteel shows that the cited art falls far short of the statutory standard of 35 USC Section 102(b). None of the rejected claims are anticipated by the Bacon and Parker references. Withdrawal of the instant rejection under Section 102(b) is therefore respectfully requested.

(ii) 35 USC 103(a) Rejections

The Examiner has rejected Claims, 5, 8, 9, 11, 12, 14-16, 53, 56, 57, 60-62 under 35 USC 103(a) as allegedly rendered obvious by each of Bacon and Parker. Applicants respectfully submit that these references do not teach or suggest the claimed invention. The Examiner has alleged that " it would have been obvious to one of ordinary skill in the art at the time the invention was made to immobilize the luminescent compound on silica particles because silica particles are well known in this art for immobilizing desired compounds." The Examiners has further alleged that "no novelty is seen in the analyte being any particular type of cell or known redox enzyme system where the method of

measuring is known for the same function as claimed and would have the expected results." Applicant respectfully submit that the Examiner is mistaken.

Applicants have fully commented on the deficiencies of Bacon and Parker above. Applicants further note that Bacon does not use, teach, or even refer to biological reactions that depend on oxidative processes, and certainly not those that use oxidative enzymes. Bacon discloses a variety of interfering substances that can affect the measurements adversely. Thus one of ordinary skill in the art would not be able to achieve the claimed invention by the teachings of Bacon. Furthermore as stated above, the disclosure of Parker directly teaches away from the subject matter of the claimed invention.

Neither Bacon nor Parker, alone or in combination, teach immobilized fluorophores for measurement of enzyme-based or cellular-based oxidative reactions in solution and by way of comparing a luminescent property to that of a control as in the Claims 5, 8, 9, 11, 12, 14-16, 53, 56, 57, 60-62. Based on the teachings of Parker, one of ordinary skill in the art would not expect success with multi-enzymatic or cellular systems in solution because the reference teaches that a single, isolated enzyme requires immobilization within the polymeric matrix. Such a suggestion renders the teachings of Parker unsatisfactory for the intended purpose of the present invention.. One of ordinary skill in the art would therefore not be led to believe in any likelihood of success by either of Bacon or Parker.

The instant application provides for determining the presence or absence of multi-enzymatic- or cellular-redox systems by way of a control. For example, there are situations in which one would desire to establish the viability of a sample of cellular or multi-enyzmatic systems prior to determining any metabolizing activity by added chemicals, drugs or toxins. The P450 system is consistent with this situation, for example. This instant application and the claimed methods provide for indirect assay of multi-enzymatic- or cellular-redox systems where this background consumption of oxygen may occur. The prior art of record clearly does not teach or suggest such methods or the advantages thereof. Withdrawal of the instant rejection is thus respectfully requested.

(iii) Section 112 Rejections

The Examiner has rejected Claims 1-16 and 49-62 under 35 USC Section 112, second paragraph. In order to advance prosecution, the following amendments have been made. The Examiner's rejection of claim 1 with regard to antecedent basis of "the presence" has been addressed by amendment. The Examiner's rejection of Claim 1 with regard to "capable of" has been addressed by amendment. The Examiner's rejection of Claim 1 with regard to "increase" in context has been addressed by amendment. The Examiner's rejection of the preamble of Claim 1 has been addressed by amendment. Applicants have also amended Claim 49 in similar fashion.

In order to further advance prosecution, Applicants have cancelled Claim 13, and Claims 17-48 and 63-90. Additionally, in order to further clarify the subject matter of the present invention, Applicants have added Claims 91-102, which are fully supported in the Specification. The biomaterial referred to in Claim 91, by way of example, is supported within the specification[3], as being any matrices that "...does not hinder the ability to gain information on oxygen concentration". One such biomaterial disclosed in the instant application is MATRIGEL™ (Example 25 & 26 and Figures 17 &18). [Other examples of "biomaterials" are listed in Table 12 under the column heading of "Supplements"] It should be appreciated that particular biomaterials may be selected for a particular cell line, the selection thereof would be within the skill of one practicing the art. BD Matrigel Matrix is composed of laminin, collagen IV, entactin, and heparan sulfate proteogylcan. It also contains growth factors, matrix metalloproteinases, and other components[4]. Thus the composition of MATRIGEL provides an example of a biomaterial that one skilled in the art would appreciate. A solution at 4°C, BD Matrigel Matrix gels at room temperature to form a three-dimensional reconstituted basement membrane. The function

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[3] See p. 24, lines 14-19. "Another feature of these sensor plates is that they may be combined with additional biomaterials such as one or more extracellular matrices, such as, for example, collagen. Assays using the matrix MATRIGEL® with various cell lines are shown in Figures 17-18. These results indicate that coating the oxygen sensor plates with extracellular matrices does not hinder the ability to gain information on oxygen consumption."

[4] http://www.bdbiosciences.com/discovery_labware/Products/cell_environments_and_ECMs/extracellular_matrix/

of a MATRIGEL matrix system is to closely mimic the structure, composition, physical properties, and functional characteristics of a basement membrane *in vivo*. Thus one skilled in the art would readily appreciate the function of such a biomaterial. Withdrawal of the present rejection is therefore respectfully requested.

(iv) Examiner's Objection

In the Official Action, the Examiner has suggested a new title for the application. Applicants respectfully traverse this objection on the grounds that the present title is generally consistent with the spirit and scope of the subject matter of the present application and complies with 37 CFR 1.72 (a).

Conclusions

(i) Since each and every element required by the claims are not taught by the prior art of record, withdrawal of the Section 102(b) rejections in view of each of Bacon and Parker is respectfully requested.

(ii) Since each of Bacon and Parker do not teach or suggest the present invention as claimed, withdrawal of the Section 103 rejection is respectfully requested.

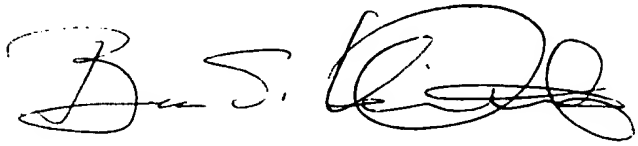
(iii) Since Claims 1 and 49 have been amended, withdrawal of the rejection under Section 112 is respectfully requested.

(iv) Since Applicants have explained why the present title of the invention is proper, withdrawal of the instant objection is respectfully requested.

Thus in view of the above Remarks and Amendments, it is believed that the present application is in condition for allowance, which action is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

Respectfully submitted,



Bruce S. Weintraub
Attorney for the Applicant(s)
Registration No. 34,277

Becton Dickinson and Company
1 Becton Drive
Franklin Lakes, New Jersey 07417
(201) 847-7096

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. A method for determining [the] presence or absence of oxidative reactions catalyzed by at least one enzyme in a solution comprising:

(i) contacting said solution with a sensor composition which comprises a luminescent compound that exhibits a change in luminescent property, when irradiated with light containing wavelengths which cause said compound to luminesce, upon exposure to oxygen, wherein the presence of the sensor composition is non destructive to [the] said [enzyme(s)] at least one enzyme;

(ii) irradiating said sensor composition with light containing wavelengths which cause said luminescent compound to luminesce;

(iii) measuring or visually observing the luminescent [light intensity] property from said luminescent compound while irradiating said sensor [compound] composition with said light;

(iv) comparing said measurement to that of a control [not containing enzyme(s) capable of catalyzing oxidative reactions], wherein said control is selected from the group consisting of:

a reagent control [not in contact with said enzyme(s)] not containing at least one enzyme capable of catalyzing said oxidative reactions and a calculated threshold, wherein a change in luminescent property relative to luminescent property of the control is indicative of the presence or absence of said [enzyme(s)] at least one enzyme; and

(v) in the event that no [such increase] change in luminescent property relative to luminescent property of the control is measured or observed, repeat steps (ii), (iii), (iv) as needed, to determine the presence or absence of said [enzyme(s)] oxidative reactions in said solution.

49. A method for determining [the] presence or absence of oxidative reactions catalyzed by at least one enzyme in a solution comprising:

(i) placing said solution in a container in which said fluid is substantially isolated from atmospheric oxygen and placing within said container, but not in direct contact with said fluid, a sensor composition which comprises a luminescent compound that exhibits a change in luminescent property, when irradiated with light containing wavelengths which cause said compound to luminesce, upon exposure to oxygen, wherein the presence of the sensor composition is non-destructive to [the] said [enzyme(s)] at least one enzyme;

(ii) irradiating said sensor composition with light containing wavelengths which cause said luminescent compound to luminesce;

(iii) measuring or visually observing the luminescent [light intensity] property from said luminescent compound while irradiating said sensor [compound] composition with said light;

(iv) comparing said measurement to that of a control [not containing said enzyme(s)], wherein said control is selected from the group consisting of:

a reagent control [not in contact with said enzyme(s)] not containing at least one enzyme capable of catalyzing said oxidative reactions and a calculated threshold, wherein a change in luminescent property relative to luminescent property of the control is indicative of the presence or absence of said [enzyme(s)] oxidative reactions; and

(v) in the event that no [such increase] change in luminescent property relative to luminescent property of the control is measured or observed, repeat steps (ii), (iii), (iv) as needed, to determine the presence or absence of said [enzyme(s)] oxidative reactions in said solution.